DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
1401 Rockville Pike
Rockville MD 20852-1448

MEMORANDUM to BLA File 98-0369

DATE: September 21, 1998

FROM: Kurt Stromberg, MD, BLA Committee Member, DCB, OTRR, CBER

TO: Julia Goldstein, MD, BLA Chairperson, DMA, OTRR, CBER

THROUGH: David Finbloom, M.D., Chief, DCB, OTRR, CBER

SUBJECT: BLA 980369: Herceptin, for treatment of advanced breast carcinoma with p185-HER2 over-expression. Anti-proliferation Assay for Biological Potency and Stability Determination

Attached is my review of this product's biopotency assay. I recommend approval.

The two in vitro biological properties for Herceptin are antibody-dependent cell-mediated cytotoxicity and antiproliferation activities. The former ADCC assay is inappropriate because it requires fresh donor cells. An advantage of the latter is that cell surface binding examines both HER2 down-regulation and interruption of mitogenesis Hence, biological potency of Herceptin is ascertained by an anti-proliferative assay using ——— which over-express the p185 HER2 protein by about twenty-fold compared to normal breast epithelial cells. This assay was able to differentiate several product variants in respect to biological activity and under the stress conditions of heat and luminosity, and consequently is used as the lot release potency test.

The final version is a ——— assay in which a standard

———

——— . (Test Procedure Q12333, BT-474 Antiproliferation Assay for rhuMAb HER2, Items 4.A.6, Vol. 8, P 132-141 and 4.A.7, Vol. 9, P164-187). A large number of variability parameters (eg., ———

——— etc., Table 1-7, Item 4, Vol. 9, P178-184) was measured. The overall relative standard deviation (RSD) was ———

During the early June, 1998 inspection, discussions with the lead inspector and BLA Chairperson, Julia Goldstein, M.D. and Genentech representatives resulted in two improvements to the potency assay. First, there are to be ———

——— for determination of activity, and secondly, an adequate

cell bank will be established for the ——————————— that is the cell basis of the assay.

The ability of this potency assay to indicate loss of biological activity under conditions of thermal, mechanical, light exposure, oxidative and pH stress (Table 8, Item 4, Vol. 9, P185) indicated only a reduction in recovery to— after —— at —degrees C. Recovery was —at — at — and was — after — exposure to — footcandles. Thus, the product stability under stress appears satisfactory. Alternatively, one could of course argue that this potency assay is not highly sensitive to product degradation.

Real time stability assessment at ——— C and ——— C, carried out on — drug product lots, including the — qualification lots and assayed by the potency assay, supports a 30-month expiration dating. The — drug qualification lot is under evaluation and will be added to Item 4.A.3.e, specifications for Herceptin release and at end of shelf life.

The reference material is Lot HER1097-3 (Item 4.A.2.e) and has been assigned a potency of 100% with as specific activity of ——————— (where 1 ug = 10 units). Final Vials contain 440 mg lyophilized Herceptin. Reconstitution occurs in 30 mls WFI, for an approximate final concentration of — mg/ml for infusion in a multi-use vial that may be stored for up to 28 days at ——— C. The lot release specification for Herceptin is ——————— Units /vial. The acceptable potency range for this anti-proliferation assay thus is set about ——— which is in keeping with the acceptable ranges set for growth factors whose potency tests are ——— assays. For example, ———

In summary, the design and application of the biological potency test for Herceptin is adequate.